REMARKS

This amendment and remarks are in response to the Office Action mailed September 25, 2006 (the "Office Action"). Applicants have amended claims 1-4, 6-8, 12-19, 23, 25-27, 32-35, 38, 52, and 53, and canceled claims 5, 9, 10, 24, 28, 29, 36, 40, 41, and 44-51 in the present amendment. Claims 1, 16, 17, and 32 have been amended to specify that the methods are for immunizing a vertebrate or mammal "against a virus selected from an influenza virus and a rotavirus," to replace "DNA transcription unit" with "plasmid vector," and to insert "an influenza virus antigen or rotavirus" before "antigen." These amendments are supported by the specification as filed, e.g., at page 7, lines 12-30, and in the Examples. Dependent claims have been amended to use claim language consistent with the independent claims. No new matter has been added.

Elections/Restrictions

In the Office Action, the Examiner acknowledged Applicants' elections in the response mailed on August 29, 2006, and stated that "[u]pon further consideration, the examiner has decided to rejoin all claims" (page 2). According to the paragraph entitled "Claim Status" on page 2 of the Office Action, claims 1-56 are pending and under examination. However, in the Office Action summary on page 1, it states that claims 8-10, 14, 15, 17-31, and 39-41 are withdrawn from consideration. Applicants respectfully request that the Examiner clarify the status of the claims for the record. In the present amendment and remarks, Applicants have treated claims 1-56 as pending.

Information Disclosure Statement

According to the Office Action, "[t]he Information Disclosure Statements (IDS) filed on 22 January 2004 and 6 July 2004 consisting of 5 sheets are in compliance with 37 CFR 1.97. Accordingly, examiner has considered the Information Disclosure Statements" (page 3).

However, many of the references listed on the Forms-1449 enclosed with the Office Action are lined through and not initialed. In the margin next to the lined through references, it

states "reference not provided." As noted on the IDS filed January 22, 2004, the present application is a continuation of U.S. application serial number 08/187,879, filed on January 27, 1994. Copies of the lined through references were not provided with the IDS because they were cited in applications to which the present application claims priority. In these circumstances, copies need not be submitted. See 37 C.F.R. § 1.98. Applicants respectfully request that the Examiner consider the references and return an initialed copy of the Forms-1449 (an extra copy of which is enclosed, for the Examiner's convenience).

Rejections Under 35 U.S.C. § 112, Enablement

Claims 1-56 were rejected as allegedly lacking enablement. In the Office Action, the scope of enablement for plasmid vectors, route of administration, and human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) DNA vaccines were each discussed separately.

Scope of Enablement for Plasmid Vectors

> According to the Office Action (at page 4, emphasis in original), the specification, while being enabling for an [sic] a method of DNA vaccination against infectious agents using a plasmid vector for administration of transcription unit(s) encoding desired antigen(s), does not reasonably provide enablement for similar methods that use viral vectors.

Applicants disagree with the remarks in the Office Action suggesting that the specification gives guidance only for plasmid systems. Nonetheless, in the interest of moving this application to allowance, and without prejudice, this rejection has been met by the amendment of the claims to recite plasmid vectors. Enablement for plasmid vectors was acknowledged by the Examiner.

Scope of Enablement for Route of Administration

The Office Action stated (at page 7):

> [c]laims 1-56 are rejected…because the specification, while being enabling for some methods of DNA vaccination using intravenous, intramuscular, intraperitoneal, intradermal and subcutaneous routes of administration, does not reasonably provide enablement for all routes of administration (page 6).
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> ***
>
> The breadth of the presently pending claims encompasses routes of administering DNA vaccines, including intravenous, intramuscular, intraperitoneal, intradermal and subcutaneous. The working examples of the instant application only demonstrate the use of (1) IV, IM, and gene gun (intradermal) combination vaccination for HIV antigens in mice, (2) gene gun (intradermal) for rotavirus antigens in mice, (3) IV, IP, SC, intratracheal, intrabursal, intraorbital for influenza antigens in fowl, (4) IV, IP, IM, intranasal, ID SC routes for influenza antigens in mice, (5) IM for influenza antigens in ferrets, (6) ID for influenza antigens in ferrets, (7) IV, IM, ID for SIV in monkeys. It appears that the inventors have tested several routes of administration, and induced certain degree [sic] of protection, particularly for influenza. However the results for influenza cannot be extended to all types of infectious agents such as HIV, to achieve a clinically beneficial effect.

In addition to these remarks, the Office Action listed brief excerpts from three articles: McCluskie et al. (*Mol. Med.*, 5:287-300, 1999; "McCluskie"), Torres et al. (*J. Immunol.*, 158:4529-4532, 1997; "Torres"), and Nakano et al. (*J. Virol.*, 71:7101-7109, 1997; "Nakano"). After listing the excerpts, the Office Action concluded that "additional and undue experimentation would be required by others in order to make and use the invention for all routes of administration, in particular for HIV" (page 8).

To the extent that the amendment of the claims does not overcome this rejection, it is respectfully traversed. The claims, as amended, do not apply to immunization against all types of infectious agents. Lack of enablement was stated to apply, in particular, to HIV. HIV is not recited in the present claims. The claims are directed to methods of immunizing vertebrates against a virus selected from an influenza virus and a rotavirus. The methods include administering to a vertebrate a plasmid vector that includes DNA encoding an influenza antigen or a rotavirus antigen linked to DNA which is a promoter region. The Office Action acknowledges the numerous routes of administration demonstrated in the working examples of the specification. These working examples are extensive and support the breadth of the claims.

McCluskie, Torres, and Nakano do not indicate that undue experimentation would have been required to make and use the invention for all routes of administration. The Office Action quoted the following sentences from the abstract of McCluskie:

> Routes of administration of plasmid DNA vaccines influences the strength and nature of immune responses in mice and non-human primates. However, the results in mice were not always predictive of those in monkeys and this is likely true for humans as well. Optimal dose and immunization schedule will most likely vary between species. It is not clear whether results in non-human primates will be predictive of results in humans, thus additional studies are required.

McCluskie administered DNA encoding a hepatitis B antigen to mice and rhesus monkeys and observed qualitative and quantitative differences in immune responses to the antigen in each species. DNA vaccination by all three routes of administration tested in the experiments induced antigen-specific immune responses in monkeys (see, e.g, McCluskie, Fig. 3, and carryover paragraph at pages 294-295). This reference does not indicate that undue experimentation would be required to practice the claimed methods. It merely reports differences in efficacy in vaccination for a particular antigen in two animal models.

Similarly, the findings reported in Torres do not at all indicate that undue experimentation is required to practice the claimed methods. Torres examined the dynamics of immune responses in animals injected with DNA in skin and muscle. Torres' data indicate that initial immunostimulatory events in skin-injected animals occurred at the site of injection, whereas immunostimulatory events in muscle-injected animals occurred in distal tissue (Torres, page 4531, right column). Nothing in the reference indicates that a particular route of administration will be unsuccessful at raising immune responses. If anything, Torres indicates that multiple routes of injection are feasible. For example, Torres stated that their data show that "the longevity of DNA-raised [antibody] responses is not dependent on long term [antigen] expression at the target site...the longevity of responses appears to be determined by events that are taking place outside of the target site" (page 432, left column, second full paragraph). Thus, according to Torres, the site of injection does not determine whether or not a long-term response is raised.

Nakano reports that intraepidermal injection of DNA encoding hepatitis antigens induced higher antibody titers than intramuscular injections. This does not establish that the claimed methods would require undue experimentation. The authors of the reference do not conclude that intramuscular administration does not work or cannot be optimized. They just note that it was less efficient in their experiments. Applicants have shown that intramuscular administration produces immune responses, including responses that provide protection against pathogens. See, e.g., Example 4, Table 6, of the specification, which shows that 18/19 mice administered DNA expressing an influenza antigen by an intramuscular route survived a lethal dose of influenza virus. Similar experiments were not performed by Nakano. Nothing in the reference shows that multiple routes of administration cannot be used to induce immune responses, and Applicants have successfully practiced immunization methods by multiple routes. If the Examiner intends to maintain the rejection, Applicants request that he state which routes of administration are and are not considered to be enabled, so that Applicants can more fully address the rejection.

Scope of Enablement for HIV and SIV Vaccines

The Office Action stated that undue experimentation would have been required to use the claimed invention to elicit protective immunity against SIV or HIV infection (page 10). The claims, as amended, do not refer to SIV or HIV. Therefore, this part of the rejection is moot.

Rejections Under 35 U.S.C. § 102

Dyall-Smith et al., U.S. Pat. 5,332,658

Claims 1, 4, 5, 8, 14, 16, 17, 24, 27, and 30-31 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Dyall-Smith et al. (U.S. Pat. 5,332,658; "the '658 patent").[1] The '658 patent is not citable as prior art under § 102(b). Nonetheless, Applicants offer the following remarks.

[1] A reference is citable as prior art under § 102(b) if it was described in a printed publication more than one year prior to the date for application for patent in the U.S. The '658 patent published on July 26, 1994, which is after the priority date of the present application. Therefore, the '658 patent is not citable as prior art under § 102(b). The '658 patent was filed as a continuation of U.S. Serial No. 07/473,959, which is the national stage application of PCT/AU88/0029. PCT/AU88/0029 published as WO 89/01514 on February 23, 1989, and is thus § 102(b) prior art.

The Office Action stated that

> Dyall-Smith et al. teach "human rotavirus gene encoding the major outer capsid glycoprotein (VP7) of the human rotavirus" (abstract). Dyall-Smith further teach the "vaccine may comprise the isolated gene, or a portion or subunit thereof, in accordance with the present invention, inserted into a viral vector such as adenovirus or vaccinia." (column 3, lines 1-4). Dyall-Smith et al. teach rotavirus antigens that "elicit protective immunity." (column 1, line 39). (page 11).

The claims are directed to methods of immunizing a vertebrate against a rotavirus or an influenza virus by administering a plasmid DNA that includes DNA encoding an influenza or rotavirus antigen operatively linked to DNA which is a promoter region, whereby a humoral immune response, cell mediated immune response, or both a humoral and cell mediated response, are elicited against the antigen.

The '658 patent does not disclose the claimed methods. The patent describes several approaches to making vaccines, none of which involve administering plasmid DNA for immunization. At column 2, lines 47-54, the patent describes using expression vectors to produce viral polypeptides, and administering polypeptides (not DNA) as vaccines. It describes administering bacteria that express viral proteins (column 2, lines 54-68). The patent also refers to a vaccine that

> may comprise the isolated gene, or a portion or sub-unit thereof, in accordance with the present invention, inserted into a viral vector such as adenovirus or vaccinia.
>
> Bacterial or viral vaccines may employ viruses dispersed in a pharmaceutical diluent such as liquid suitable for oral administration. Alternatively the bacteria or viruses may be freeze dried and administered in a solid form. (column 3, lines 1-9).

Thus, the viral vector vaccines contemplated by the patent employ viruses (i.e., virus *particles*), not plasmid DNA. The present claims, as amended, refer to administration of plasmid DNA. The '658 patent does not disclose administration of plasmid DNA to induce immune responses. Applicants respectfully request withdrawal of the rejection of the claims as allegedly anticipated by this reference.

Eppstein et al., U.S. Pat. 5,049,386

Claims 1-6, 10-19, 21-25, 29-37, and 41-43 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Eppstein et al. (U.S. Pat. 5,049,386; "the '386 patent"). The Office Action stated (at pages 12-13, carryover paragraph):

> Eppstein et al. teach "vaccine administration…to an animal or mammal in need thereof" (column 15, lines 7-10) including "delivery of…DNA…plasmids containing promoters" (column 10, lines 15-27) that enhance "humoral and/or cellular immunity, to an antigen of interest (column 12, lines 41-42).

Applicants respectfully traverse this rejection. The claims are directed to methods of immunizing a vertebrate by administering a plasmid DNA, whereby a humoral immune response, cell mediated immune response, or both a humoral and cell mediated response, are elicited.

The '386 patent does not disclose methods of using a DNA plasmid to elicit an immune response in a mammal. In the Office Action, disparate sections of the specification of the '386 patent are quoted to allege that the subject matter of the claims is anticipated. However, when read in context, these passages do not describe or even suggest the claimed methods. The '386 patent describes liposome compositions and their use to deliver therapeutic agents. Uses of liposomes to deliver polynucleotides are disclosed at column 10, lines 15-27. However, there is no suggestion to use DNA-containing compositions for inducing immune responses. The patent discusses induction of immune responses solely in the context of protein antigens. At column 12, lines 39-48, the '368 patent states:

> Another application of certain formulations comprising the compounds of Formula I is the enhancement of a specific immune response, such as humoral and/or cellular immunity, to an antigen of interest which is incorporated in the lipid-containing vesicles. Thus, such preparations can serve as specific adjuvants for vaccines (including viral, bacterial, rickettsial, parasitic, and cancer vaccines), **antigen preparations, as well as other proteins or peptides** including synthetic peptides of interest. (emphasis added)

The "antigen preparations" in the above passage are described as a type of protein or peptide composition. Therefore, antigens refers to protein or peptide antigens, not DNA. The

patent's description of vaccine preparations makes no reference to DNA plasmids as the agent to be administered. Instead it says that "[t]he formulation of a vaccine using the compounds of Formula I described herein will employ an effective amount of antigenic material." (column 15, lines 13-15). This does not suggest uses of DNA plasmid vectors. In describing vaccine preparations, the patent states (at column 10, lines 34-36):

> It is contemplated that the lipid or liposome formulations of this invention may be used in conjunction with whole cell or virus vaccines as well as purified antigens or subunit or peptide vaccines prepared by recombinant DNA techniques or synthesis.

A subunit or peptide vaccine prepared by recombinant DNA techniques, as described in the patent, is not the same as a plasmid DNA used to elicit an immune response. Example 14 of the patent describes the preparation of particular subunit vaccines. The compositions administered in the Example which include a liposomal agent, N-(2,3-di(9-(Z)-octadecenyloxy))-prop-1-N,N,N-trimethylammonium chloride (DOTMA), and infectious bovine rhinotracheitis viral antigen, derived from the membrane glycoprotein fraction of virus infected cells (column 46, lines 59-69). The "subunit" component of this subunit vaccine is protein antigen. No other subunit vaccines are exemplified in the patent and there is no suggestion that subunit vaccines refer to compositions that include DNA. Where DNA administration is discussed, there is no suggestion to use it for inducing immune responses. Administration of DNA to living subjects is discussed in the context of treating genetic disorders (column 19, lines 43-51) and replacing factors in the body such as hormones, blood coagulation factors, and deficient enzymes (column 10, lines 43-65), but not vaccination. The '386 patent does not disclose any methods of immunizing a vertebrate by administering plasmid DNA, whereby a humoral immune response, cell mediated immune response, or both a humoral and cell mediated response, are elicited. Therefore, the '386 patent does not anticipate claims 1-5, 11-19, 21-23, 30-35, 37, 42, and 43.[2] Withdrawal of this rejection is respectfully requested.

[2] Claims 5, 10, 24, 29, 36, and 41, are canceled by the present amendment.

Obviousness-Type Double Patenting

Claims 1-2, 4-7, 11-13, 16, 32-34, 36-38, 42, 43, 52, and 53 were rejected under the doctrine of obviousness-type double patenting as unpatentable over claims 1-19 of U.S. Pat. No. 5,643,578. Upon an indication that the present claims are otherwise in condition for allowance, Applicants will submit an appropriate terminal disclaimer.

CONCLUSION

Applicants submit that the claims are in condition for allowance and such action is requested. Please apply the Petition for Two-Month Extension of Time fee and any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 07917-217002.

Respectfully submitted,

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